Eur J Vasc Endovasc Surg (2010) **39**, 577–585

Characteristics and Outcome of Patients Hospitalised for Lower Extremity Peripheral Artery Disease in France: The COPART Registry

J.P. Cambou [a,*], V. Aboyans [b,c], J. Constans [d], P. Lacroix [b,c], C. Dentans [e], A. Bura [a,f]

[a] *Department of Vascular Medicine, Rangueil University Hospital, Toulouse, France*
[b] *Department of Thoracic and Cardiovascular Surgery and Vascular Medicine, Dupuytren University Hospital, Limoges; France*
[c] *EA3172 Limoges University, Limoges, France*
[d] *Department of Vascular Medicine, Saint-André Hospital, Bordeaux, France*
[e] *INSERM U 558, Epidémiologie et analyses en santé publique; Toulouse, France*
[f] *INSERM U858, Toulouse, France*

Submitted 19 October 2009; accepted 16 February 2010
Available online 19 March 2010

KEYWORDS
Outcomes;
Peripheral artery disease;
Registry;
Study design

Abstract *Objectives:* To assess the current 'real-world' management of hospitalised patients with lower-extremity peripheral artery disease (LE-PAD) and to assess the 1-year outcome.
Design, materials and methods: The prospective and multicentre registry *COhorte des Patients ARTériopathes* (COPART) recruited consecutive patients from the departments of vascular medicine of three academic hospitals in Southwestern France.
Results: Among the 940 patients, 27.4% had intermittent claudication (IC), 9.3% ischaemic rest pain, 54.3% ulceration or gangrene and 9.3% acute limb ischaemia (ALI). Patients with IC were younger and more likely to be men, with a history of smoking (89.5%) and chronic obstructive pulmonary disease (17%). Among those with IC, 8.9% had bypass surgery and 41.5% were treated with percutaneous angioplasty. Those with tissue loss had higher rates of cardiovascular disease (CVD) risk factors and co-morbidities. At entry to the study, the level of control of the CVD risk factors was poor. The 1-year mortality rate was of 5.7% in patients with IC, 23.1% in patients with ischaemic rest pain, 28.7% in patients with tissue loss and 23% in those with ALI. Compliance with evidence-based medicine and pharmacological treatment was sub-optimal.

* Corresponding author. Service de Médecine Vasculaire, Hôpital Rangueil, 1, avenue du Professeur Jean Poulhès, TSA 50032, 31059 Toulouse, France. Tel.: +33 5 61 32 24 38; fax: +33 5 61 32 26 34.
E-mail address: jean-pierre.cambou@orange.fr (J.P. Cambou).

doi:10.1016/j.ejvs.2010.02.009

Conclusion: This registry underscores the differences in patient profiles in the daily clinical setting, compared to those enrolled in several trials.

As a manifestation of atherosclerosis, lower-extremity peripheral artery disease (LE-PAD) is a source of disability, mostly when it becomes clinically manifest, and it is often associated with other cardiovascular diseases (CVDs).[1] In addition to the risk of limb loss and disability, the general prognosis is poor, due to the high risk of concomitant coronary artery disease (CAD) and cerebrovascular disease (CBVD) and the occurrence of fatal- and non-fatal CVD ischaemic events.[2–4]

Data on epidemiology of LE-PAD in France are scarce. Large registries comprising patients with LE-PAD are very few,[5–10] particularly with regard to hospitalised patients affected by LE-PAD.[11,12] Overall, data available on the natural history of LE-PAD are mostly issued from studies including patients with intermittent claudication. Few studies have been performed in the field of ischaemic rest pain or tissue-loss LE-PAD, especially in the modern area of efficient preventive drug therapies (statins and renin–angiotensin system (RAS) inhibitors), as well as the increasing use of distal re-vascularisation procedures.

Hospital registries allow the collection of epidemiological data on a specific disease and scientific data on the impact of different therapeutic approaches. In addition, they provide a better understanding of the degree of application of guidelines in the management of the disease.

The *COhorte de Patients ARTériopathes* (COPART) is a registry collecting exhaustive data on all patients hospitalised for LE-PAD. This registry aims to improve knowledge on the management of clinical LE-PAD in France and to report the prognosis of these patients after discharge.

Materials and Methods

The COPART registry is a prospective multicentre study. Patients were consecutively recruited initially from the department of vascular medicine of Rangueil Hospital, University of Toulouse, since June 2004. The registry has been extended to the departments of vascular medicine in Bordeaux (Saint-André Hospital, Bordeaux University) and Limoges (Dupuytren University Hospital) since October 2006. In each centre, care to patients was provided according to the usual practice without any change in management strategy.

Inclusion criteria

To be included, each patient needed to meet the following criteria: age >18 years, consent to participate into the study and referred to the hospital specifically for clinical LE-PAD of atherosclerotic origin. The clinical stages were to be either intermittent claudication (IC), associated with an abnormal ankle–brachial index (ABI) <0.90 or >1.30 or, in case of a normal ABI at rest, a positive treadmill test (Strandness protocol) and/or an arterial stenosis >50% revealed by duplex ultrasound and/or angiography, or ischaemic rest pain or ulceration and gangrene[4] or acute lower-limb ischaemia, related to a documented LE-PAD with significant arterial stenosis. Cases with acute ischaemia following bypass surgery or endovascular procedures were also included.

Exclusion criteria

Patients whose follow-up was considered improbable, those with arterial occlusive disease not related to atherosclerosis (endofibrosis, inflammatory arterial disease, Buerger's disease, entrapment syndromes, etc.), those with acute ischaemia without lower-limb atherosclerosis (embolic) and patients refusing to participate were excluded from the study.

Data collection

A computerised case-record form was filled-in for each patient. The initial characteristics and the clinical and therapeutic data on admission, during hospitalisation and at discharge were collected. Similarly, clinical events occurring during hospitalisation and within the first year of follow-up were collected. The data collected at admission included age, gender, CVD risk factors and LE-PAD clinical presentation according to the Rutherford classification.[13] CVD risk factors were defined as follows: diabetes was defined by documented medical history, the use of oral anti-diabetic agents or insulin or fasting plasma glucose levels ≥1.26 g l; dyslipidaemia was defined by a documented medical history, use of lipid-lowering agents for this purpose or fasting low-density lipoprotein (LDL)-cholesterol ≥100 mg dl; hypertension was defined by documented medical history and use of anti-hypertensive drugs for this purpose, or systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg at admission determined by the average of the first two measurements. Patients were considered as current smokers if they were smoking at least one cigarette per day. Patients were considered past-smokers if they had stopped smoking since at least 1 month prior to inclusion in the study. The following CVDs were noted, according to the documented medical history: CAD heart failure, atrial fibrillation, presence of a pacemaker at admission, CBVD including ischaemic or haemorrhagic stroke as well as transient ischaemic attack. Chronic kidney disease was defined as previous history or noted according to the estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease (MDRD) Study equation, and chronic kidney disease was defined when eGFR <60 ml min^{-1} 1.73 m^{-2}.

For the follow-up, the sequential procedure consisted of consulting mortality data at registrar's offices, mailing to the family physicians and/or cardiologists/angiologists and, finally, contacting the patients themselves, if necessary.

Hospital-discharge letters were systematically sought for each event leading to hospitalisation or death and were analysed by a physician from the research group.

The primary outcome was total mortality. The secondary outcomes were amputation, re-vascularisation during the 1-year follow up and a composite outcome combining mortality, non-fatal myocardial infarction (MI) and non-fatal stroke.

Statistical analysis

For quantitative variables, means and standard deviations (SDs; or median for non-parametric data) are presented. Discrete variables are presented as numbers and percentages. Comparisons were made with chi-square test (or Fisher's exact tests, when appropriate) for discrete variables, and by Kruskal—Wallis test for continuous variables. We used a polynomial regression analysis to test differences between the three LE-PAD stages after adjustment for age.

In-hospital and 1-year survival rates after the index hospitalisation were presented as percentages and comparisons were made by chi-square tests. Kaplan—Meier survival curves were used with log-rank test to compare the 1-year mortality in different subgroups. We used the Cox regression model to assess the survival according to the LE-PAD clinical presentation.

Results

From June 2004 to October 2008, 1009 patients with LE-PAD were consecutively hospitalised in one of the three medical centres of the COPART registry. The inclusion/exclusion of hospitalised patients as well as clinical subtypes are presented in a flow-chart (Fig. 1). Overall, 940 patients were included (608 patients from Toulouse, 129 from Bordeaux and 203 from Limoges). Among them, 28 (3%) expired during the in-hospital period. Among the 912 patients alive at discharge, 649 have already reached the 1-year follow-up. Table 1 shows the study population general characteristics. Reasons for referral were IC (Rutherford grade I category 3), ischaemic rest pain (Rutherford grade II category 4), ulceration or gangrene (Rutherford Grades III—IV category 5—6) and acute limb ischaemia (ALI) for referral in 27.2%, 9.3%, 54.3% and 9.3% of cases, respectively. Almost

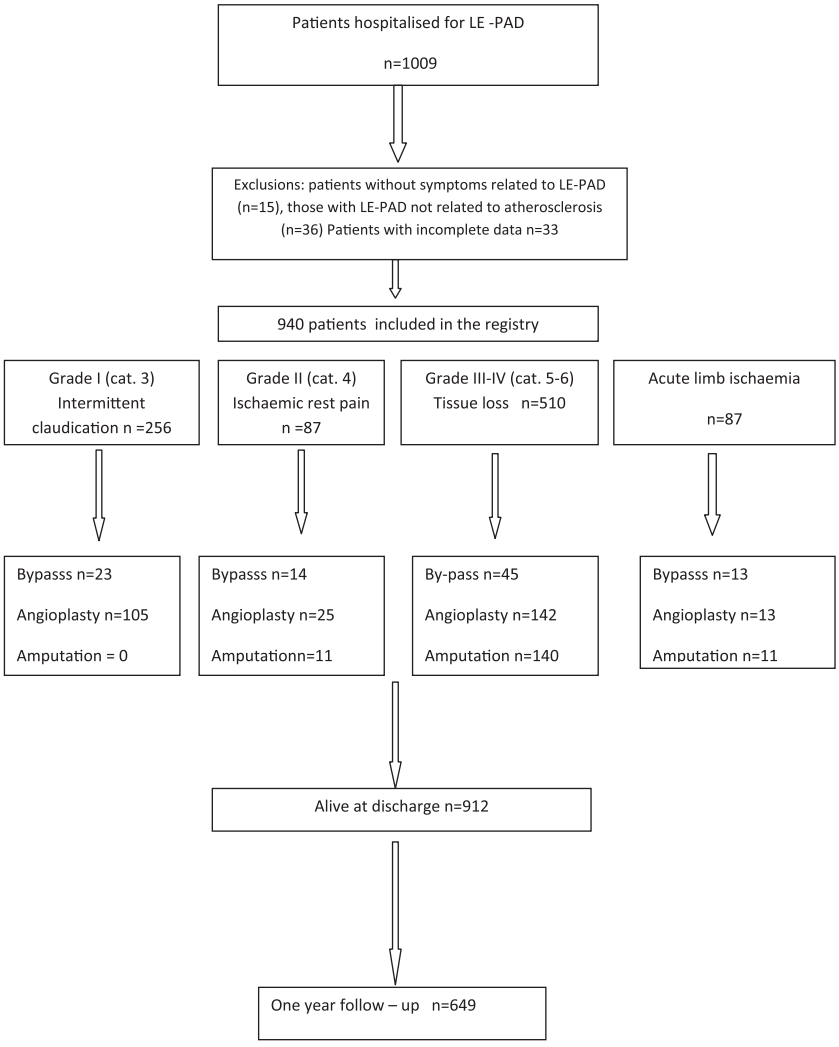


Figure 1 Flowchart of patients — the COPART registry.

Table 1 Baseline characteristics of the study population.

Characteristics (n = 940)	N (%)
Men	675 (71.8)
Age (years mean ± SD)	70.2 ± 12.8
Age ≥75 years	395 (42.0)
Previous history	
Coronary artery disease	359 (38.2)
Myocardial infarction	196 (20.9)
Cerebrovascular disease	143 (15.2)
Heart failure	112 (11.9)
Atrial fibrillation	182 (19.4)
Peripheral angioplasty	177 (18.8)
Peripheral bypass	173 (18.4)
Amputation	159 (16.9)
Chronic Kidney Disease	150 (16.0)
Cardiovascular risks factors	
Hypertension	649 (69.0)
Hypercholesterolaemia	499 (53.1)
Current smokers	232 (24.7)
Ever smokers	709 (75.4)
Diabetes mellitus	413 (43.9)
Ankle-brachial index (n = 764)	
≥1.3	96 (12.6)
≥0.9—<1.3	41 (5.4)
≥0.7—<0.9	102 (13.4)
≥0.5—<0.7	187 (24.5)
<0.5	338 (44.2)
Treatment during the hospital stay	
Bypass surgery	95 (10.1)
Angioplasty	285 (30.3)
Amputation	162 (17.2)
Drug therapies at discharge (n = 903)	
Antiplatelet agents (APA)	737 (81.6)
Aspirin	547 (60.6)
Clopidrogel	290 (32.1)
Statins	633 (70.0)
Angiotensin-converting enzyme (ACE) inhibitors	365 (40.4)
Angiotensin II-receptor blockers (ARBs)	163 (18.1)
Beta-blockers	241 (26.7)
Vitamin K antagonists (VKA)	138 (15.3)

one-half (44.2%) had an ABI < 0.50. Patients with Rutherford grades III—IV had higher rates of diabetes (60%), while patients with IC presented higher rates of dyslipidaemia and smoking (Fig. 2). A majority of these patients had symptomatic multifocal CVD (Fig. 3). Patients with Rutherford grades III—IV were more likely to have previous history of CAD and/or CBVD, although this could be partly explained by an older age.

Fig. 4 displays co-morbidities in LE-PAD patients according to the Rutherford grade. A history of heart failure was more frequent in patients with tissue loss (Rutherford grades III—IV). A history of atrial fibrillation was more frequent among participants with grades III—IV (24.1%) and ALI (27.6%).

Clinical and biological parameters at entry to the study are shown in Table 2. One out of five patients was obese. Almost one-half had elevated systolic blood pressure (47.7%). One-third had an LDL-cholesterol >100 mg dl^{-1} and 39.5% had a high-density lipoprotein (HDL)-cholesterol <40 mg dl^{-1}, especially in case of Grade IIIV. Similarly, 28.2% of the patients had an elevated blood glucose ≥1.26 g l^{-1}), mainly in the grades III—IV group.

Lower-limb angiography was performed in ∼60% of the cohort and duplex ultrasound in ∼90% during hospitalisation. Angioplasty was performed more frequently in patients with claudication (41.0%) than in ischaemic rest pain (28.7%) or tissue-loss grade patients (27.8%) The rates of bypass surgery were comparable in different clinical patterns More than one-quarter (24.8%) of patients with Rutherford Grade II—IV underwent amputation during the hospital stay (including 15.0% above the ankle; Fig. 5).

At discharge, patients with grades II to III—IV or ALI received statins, anti-platelet drugs, RAS inhibitors and beta-blockers less often than IC patients. Full preventive pharmacological therapies (statins, anti-platelet agents and RAS inhibitors) were only prescribed in 53.5% of patients with IC, 37.8% of those with ischaemic rest pain, 34.8% of those with tissue loss and 28.6% of those who presented an ALI (Fig. 6). In addition to the in-hospital mortality rate of 3%, the 1-year mortality was at 21.4%, with consistent disparities according to the LE-PAD clinical presentations (Table 3 and Fig. 7). There was no statistical difference in mortality rates according to treatment during the hospital stay: angioplasty (20.7%) and bypass surgery (24.6%). Mortality was related to CVDs in one-half of the cases. Adjusted for age, the total mortality rate was four times higher in patients with grades III—IV compared to those with grade I (hazard ratio (HR): 4.2, standard error (SE): 1.5 (range: 2.1—8.4)) and in patients with grade II (HR: 4.1, SE: 1.95 (95% confidence interval (CI): 1.6—10.3) and three times higher in patients with ALI (HR: 3.3, SE: 1.5 (1.3—8.0)).

Discussion

In this report, we present the first results of an exhaustive multicentre registry of patients managed in vascular medicine departments of three university hospitals in the southwest of France. One potential value of a registry is the provision of information about patients who are generally under-represented in randomised clinical trials, especially women (28% in our study) and very old patients (42% > 75 years in this study). In contrast to other LE-PAD cohorts,[7,9,14] 53% of the patients in this study had critical limb ischaemia (grades III—IV). Of note, the registry included only patients with IC whose clinical situation required hospitalisation. Our patients had a severe risk profile due to high rates of co-morbidities: CAD (38.4%), atrial fibrillation (18.9%) and previous history of chronic kidney disease (15%). Obviously, patients in this registry are not comparable to the outpatients with atherothrombosis enrolled in the Reduction of Atherothrombosis for Continued Health (REACH) registry.[10] Due to differences in the study design and inclusion criteria, other CVDs were more frequent in REACH than in the COPART registry. In France, a cohort of 3811 patients with LE-PAD managed by general practitioners has been reported in the ATTEST study (ArTeriopaThie oblitErante des membres inferieurS

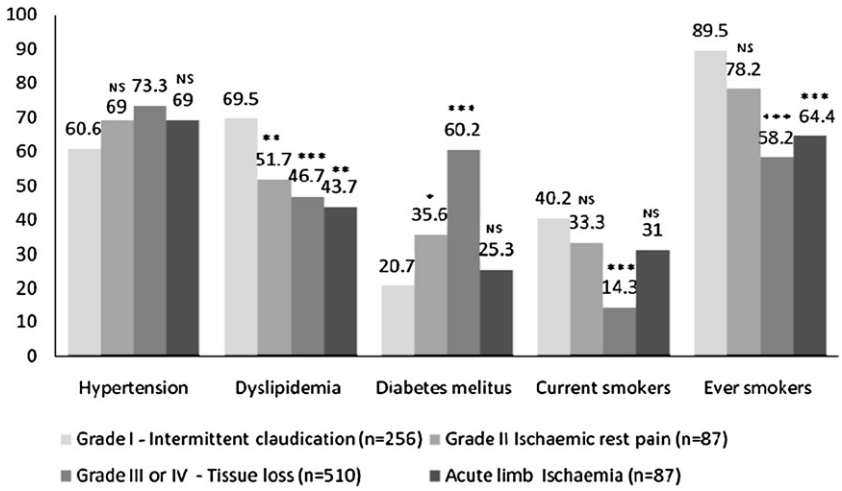


Figure 2 Cardiovascular risks factors according to the LE-PAD stages ($n = 940$) ''p'' = age adjusted p with IC taken as reference NS = non significant *p value < 0.05. **p value < 0.01 ***p value < 0.001.

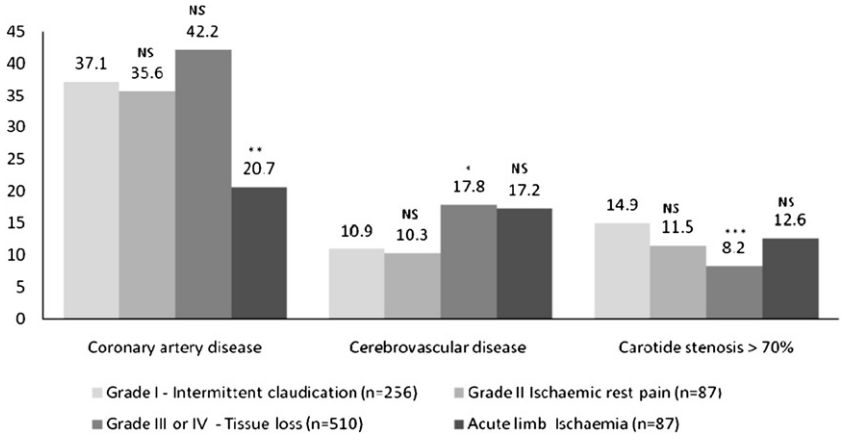


Figure 3 Coronary and cerebrovascular disease in LE-PAD patients ($n = 940$) ''p'' = age adjusted p with IC taken as reference NS = non significant *p value < 0.05 **p value < 0.01 ***p value < 0.001.

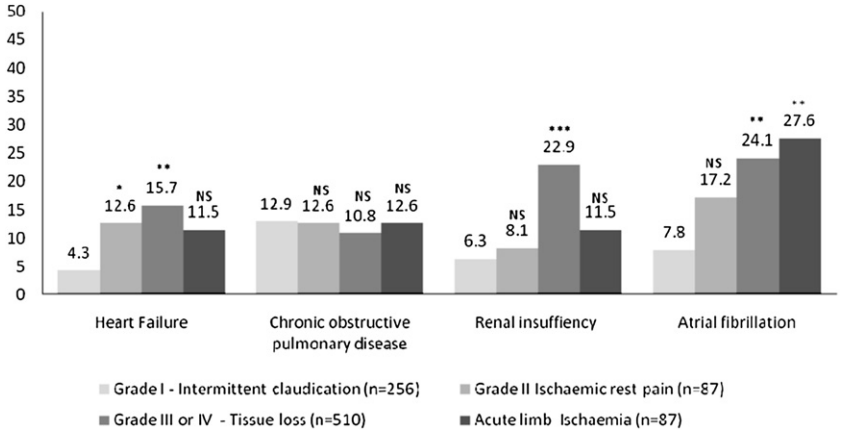


Figure 4 Co morbidity according to the LE-PAD clinical presentation groups ($n = 940$) ''p'' = age adjusted p with IC taken as reference NS = non significant *p value < 0.05 **p value < 0.01 ***p value < 0.001.

Table 2 Clinical and biological parameters at entry according to the clinical presentation.

	Grade I	Grade II	Grade III—IV	Acute limb ischaemia (ALI) *n* (%)
	Category 3 Intermittent claudication *n* (%)	Category 4 Ischemic rest pain *n* (%)	Category 5-6 Tissue loss *n* (%)	
BMI $\geq$30 kg/m^2 ($n = 713$)	39/210 (18.6)	12/66 (18.2)	81/380 (21.3)	7/57 (12.3)
SBP ($n = 922$)				
<140 mmHg	135/251 (53.8)	45/84 (53.6)	262/502 (53.0)	40/85 (47.0)
$\geq$140 < 160 mmHg	71/251 (28.3)	22/84 (26.2)	13/502 (26.1)	30/85 (35.3)
$\geq$160 mmHg	45/251 (17.9)	17/84 (20.2)	109/502 (21.7)	15/85 (17.7)
DBP ($n = 922$)				
<80 mmHg	136/251 (54.6)	51/84 (60.7)	313/502 (62.6)	48/85 (56.5)
$\geq$80 < 90 mmHg	88/251 (35.1)	23/84 (27.4)	141/502 (28.2)	22/85 (25.9)
$\geq$90 mmHg	26/251 (10.4)	10/84 (11.9)	46/502 (9.2)	15/85 (17.2)
HDL-cholesterol <40 mg/dl ($n = 537$)	47/148 (31.8)	20/49 (40.8)	172/303 (56.8)***	131/303 (43.2)
LDL-cholesterol $\geq$100 mg/dl ($n = 528$)	67/143 (46.9)	17/46 (37.0)	98/302 (32.5)*	13/37 (35.1)
Triglycerides $\geq$ 1.50 g/l ($n = 629$)	73/172 (42.4)	24/57 (42.1)	115/357 (32.2)	9/43 (20.9)**
Glycaemia $\geq$ 1.26 g/l ($n = 783$)	37/213 (17.4)	19/73 (26.0)	147/428 (34.7)*	18/69 (26.1)
CRP us $\geq$ 6.4 UI ($n = 741$)	67/169 (39.6)	42/68 (61.8)***	381/440 (86.6)***	51/64 (79.7)**
Chronic Kidney Disease ($n = 820$)	64/231 (27.7)	34/80 (42.5)	295/449 (64.5)**	34/69 (49.2)*

p = age adjusted p with grade I (IC) taken as reference.
*p value < 0.05, **p value < 0.01, ***p value < 0.001.

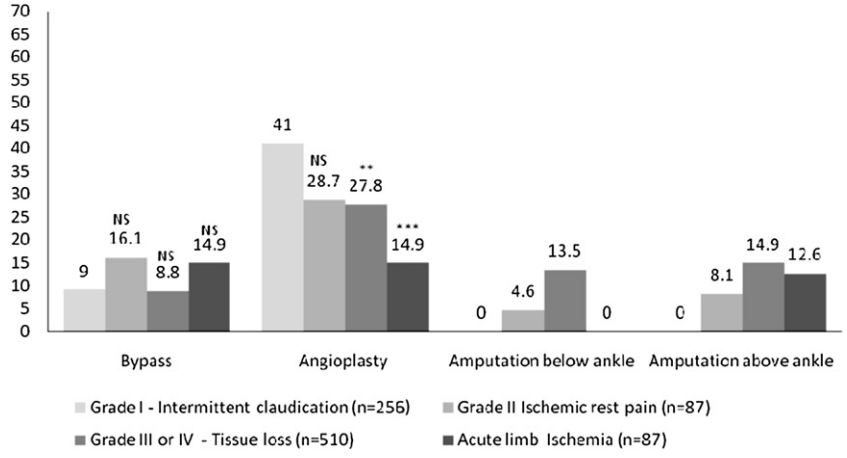


Figure 5 Treatment during the hospital stay ($n = 940$) ''p'' = age adjusted p with IC taken as reference NS = non significant *p value < 0.05 **p value < 0.01 ***p value < 0.001.

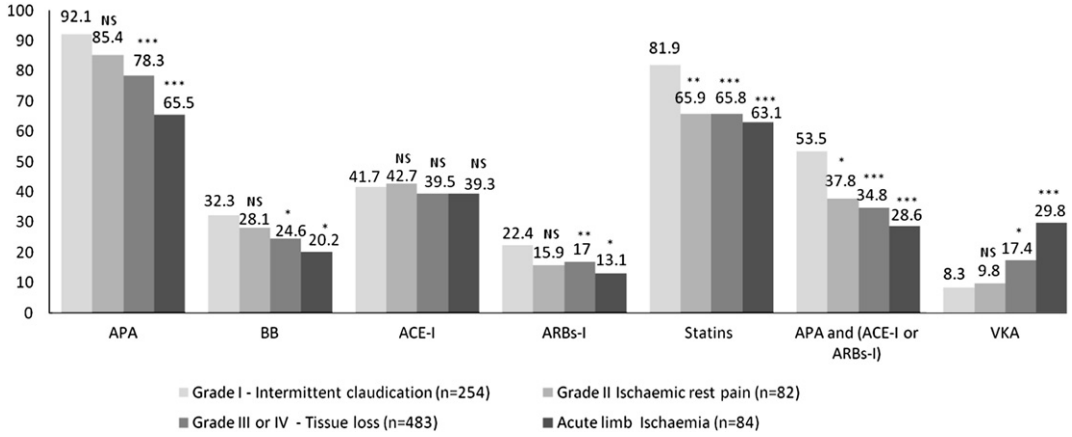


Figure 6 Treatment at discharge ($n = 903$) Patient alive at discharge and with treatment known ''p'' = age adjusted p with IC taken as reference NS = non significant *p value < 0.05 **p value < 0.01 ***p value < 0.001.

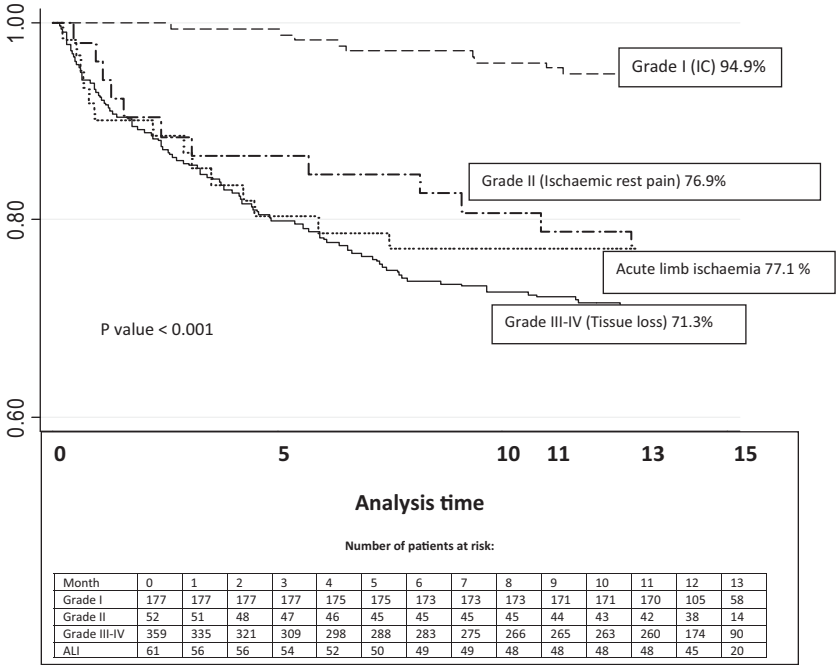
Table 3 One-year outcome $n = 649$.[a]

	Grade I	Grade II	Grade III–IV	Acute limb ischemia (ALI) *n* (%)
	Category 3 Intermittent claudication *n* (%)	Category 4 Ischemic rest pain *n* (%)	Category 5-6 Tissue loss *n* (%)	
	$n = 177$	$n = 52$	$n = 359$	$n = 61$
Total death	10 (5.7)	12 (23.1)**	103 (28.7)***	14 (23.0)**
Cardiovascular death	4 (2.3)	5 (9.6)	54 (15.0)**	9 (14.8)**
Total death or non-fatal myocardial infarction or non-fatal stroke	14 (7.9)	13 (25.0)**	109 (30.4)***	15 (24.6)*
Angioplasty or bypass surgery after discharge	21 (11.9)	11 (21.2)*	39 (10.9)	1 (1.6)
Amputation after discharge	3 (1.7)	12 (23.1)***	89 (24.2)***	9 (14.8)***

Age adjusted p value with grade I (IC) taken as reference.
*p value < 0.05, **p value < 0.01, ***p value < 0.001.
[a] Patients with a one-year follow-up.

chez les paTients en medecine génèrale).[8] Those with isolated LE-PAD (without other clinical CVD) presented higher rates of smoking and dyslipidaemia than in the COPART cohort. As a result, more diabetic and hypertensive patients are reported in COPART. The results of our registry can also be used to assess the compliance with evidence-based medicine and guidelines. Statins were given at discharge in >70% of LE-PAD patients, anti-platelet agents were commonly used, but the prescription of angiotensin-converting enzyme (ACE)-inhibitors and beta-blockers were sub-optimal. The evidence-based therapies (statins, anti-platelet agents and RAS inhibitors) were fully prescribed in only 40% of the patients. Regarding the use of anti-platelet therapies, these non-conformities were partly explained by different rates of use of vitamin-K antagonists (VKAs). Paradoxically, the use of these therapies was even lower in more severe cases of LE-PAD, with grades II–IV of disease. The rate of use of these major therapies was even lower in the Dutch cohort of hospitalised patients,[7] although this could be explained by the fact that the latter enrolled the patients from 1990 to 2005, before the LE-PAD international guidelines.[4] The prescription rates of these four major drug groups in COPART are quite similar to the French arm of the REACH registry.[10] Conversely, higher rates of use of beta-blockers are reported in the REACH registry (49.3% vs. 26.7%)

In our study, the prognosis of patients is poor, with dramatic 1-year mortality at 21.4%, including CVD death in



Month	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Grade I	177	177	177	177	175	175	173	173	173	171	171	170	105	58
Grade II	52	51	48	47	46	45	45	45	45	44	43	42	38	14
Grade III-IV	359	335	321	309	298	288	283	275	266	265	263	260	174	90
ALI	61	56	56	54	52	50	49	49	48	48	48	48	45	20

Figure 7 One-year Kaplan Meier survival curves (Total death) according to LE-PAD stages ($n = 649$) ''p'' = age adjusted p with IC taken as reference.

one-half of the cases. In an Italian registry of patients with critical limb ischaemia,[2] the reported mortality rates (19.1%) were lower than in our grades III—IV patients (28.7%). In clinical trials comprising patients with LE-PAD,[15,16] mortality and CVD-events rates are quite also lower. In other series, including mainly patients with IC, the mortality and major cardiovascular events rates are also lower than in our registry. Actually, patients with less severe disease, requiring ambulatory medical treatment, are beyond the scope of our study. This could even explain the surprisingly high 1-year amputation rate of 1.7% in patients with IC. In contrast, the high amputation rate at 25% in the more severe LE-PAD cases is comparable to the rate in other hospital series.[4] The poor level of management of CVD risk factors at admission has also been presented in other reports.[7,14,17—20] Given the high rates of fatal and non-fatal events, further efforts should be made to improve the secondary prevention in the patients.

In conclusion, this French multicentre registry provides 'real word' data on current treatment and outcomes of LE-PAD hospitalised patients in university hospitals in France. Our results highlight important prognosis differences according to the clinical stage and the worse CVD risk profile in case of ischaemic rest pain or tissue loss, partly explained by older age of such patients. Our patients were also mostly affected by other CVDs (CADs and cerebral artery diseases) and had an unsatisfactory level of CVD risk-factors management. Their prognosis is dramatically poor. Compliance with evidence-based medicine was sub-optimal, particularly with a low level of use of RAS inhibitors. An adequate control of CVD risk factors is highly recommended to reduce the very high incidence of fatal and non-fatal events. In addition, the COPART registry underscores the differences in patients' profiles in the daily clinical setting, compared to patients with LE-PAD enrolled in several trials. As for illustration, recent findings on the lack of effectiveness of statins[21,22] in very advanced conditions, such as heart failure or end-stage renal disease, highlight the necessity to re-assess the major therapies used for the secondary prevention in the specific field of progressed LE-PAD, especially in case of rest pain ischaemia or tissue-loss LE-PAD group.

Ethical Approval for Research

Not required for observational studies in France.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Authors Contribution

Conception and design; JC, PL, JPC, VA.
Analysis and interpretation: CD, JPC, VA
Data collection: JC, PL, ABR, JPC,VA.
Writing the article: JPC, VA.
Critical revision of the article: ABR, JC, PL, JPC, VA, CD.
Statistical analysis: CD, JPC.
Overall responsibility: ABR, JC, PL.

Acknowledgements

The COPART registry is supported by the French Vascular Medicine Society (SFMV) and by grants from AstraZeneca France, Bayer France, Bristol—Myers—Squibb France and Sanofi—Aventis France companies.

We thank the research-assistants team: Delphine Baudoin, Djamel Kerfellah, Emmanuelle Lorian, Béatrice Montalegre and Monique Paillol.

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